An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction

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CONTENTS

***Background*: Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that occurs as a result of exercise. EIB occurs in a substantial proportion of patients with asthma, but may also occur in individuals without known asthma.**

***Methods*: To provide clinicians with practical guidance, a multidisciplinary panel of stakeholders was convened to review the pathogenesis of EIB and to develop evidence-based guidelines for the diagnosis and treatment of EIB. The evidence was appraised and recommendations were formulated using the Grading of Recommendations, Assessment, Development, and Evaluation approach.**

***Results*: Recommendations for the treatment of EIB were developed. The quality of evidence supporting the recommendations was variable, ranging from low to high. A strong recommendation was made for using a short-acting β_2-agonist before exercise in all patients with EIB. For patients who continue to have symptoms of EIB despite the administration of a short-acting β_2-agonist before exercise, strong recommendations were made for a daily inhaled corticosteroid, a daily leukotriene receptor antagonist, or a mast cell stabilizing agent before exercise.**

***Conclusions*: The recommendations in this *Guideline* reflect the currently available evidence. New clinical research data will necessitate a revision and update in the future.**

EXECUTIVE SUMMARY

Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that occurs as a result of exercise. A substantial proportion of patients with asthma experience exercise-induced respiratory symptoms. EIB has also been shown to occur in subjects without a known diagnosis of asthma.

Diagnosis

- The diagnosis of EIB is established by changes in lung function provoked by exercise, not on the basis of symptoms.
- Serial lung function measurements after a specific exercise or hyperpnea challenge are used to determine if EIB is present and to quantify the severity of the disorder. It is preferable to assess FEV_1, because this measurement has better repeatability and is more discriminating than peak expiratory flow rate.
- The airway response is expressed as the percent fall in FEV_1 from the baseline value. The difference between the pre-exercise FEV_1 value and the lowest FEV_1 value recorded within 30 minutes after exercise is expressed as a percentage of the pre-exercise value. The criterion for the percent fall in FEV_1 used to diagnose EIB is $\geq$10%.
- The severity of EIB can be graded as mild, moderate, or severe if the percent fall in FEV_1 from the pre-exercise level is $\geq$10% but $<$25%, $\geq$25% but $<$50%, and $\geq$50%, respectively.
- A number of surrogates for exercise testing have been developed that may be easier to implement than exercise challenge. These surrogates include eucapnic voluntary hyperpnea or hyperventilation, hyperosmolar aerosols, including 4.5% saline, and dry powder mannitol.

Treatment

- For patients with EIB, we recommend administration of an inhaled short-acting β_2-agonist (SABA) before exercise (*strong recommendation*, *high-quality evidence*). The SABA is typically administered 15 minutes before exercise.
- A controller agent is generally added whenever SABA therapy is used daily or more frequently.
- For patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently:
  - We recommend *against* daily use of an inhaled long-acting β_2-agonist as single therapy (*strong recommendation*, *moderate-quality evidence*). This is based upon a strong concern for serious side effects.
  - We recommend daily administration of an inhaled corticosteroid (ICS) (*strong recommendation*, *moderate-quality*

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evidence). It may take 2–4 weeks after the initiation of therapy to see maximal improvement.

- We recommend *against* administration of ICS only before exercise (*strong recommendation*, *moderate-quality evidence*).
- We recommend daily administration of a leukotriene receptor antagonist (*strong recommendation*, *moderate-quality evidence*).
- We recommend administration of a mast cell stabilizing agent before exercise (*strong recommendation*, *high-quality evidence*).
- We suggest administration of an inhaled anticholinergic agent before exercise (*weak recommendation*, *low-quality evidence*).
- In our clinical practices, we generally add a daily inhaled ICS or a daily leukotriene receptor antagonist first, with the choice between these agents made on a case-by-case basis depending upon patient preferences and baseline lung function. Mast cell stabilizing agents and inhaled anticholinergic agents play a secondary role.

- For patients with EIB and allergies who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we suggest administration of an antihistamine (*weak recommendation*, *moderate-quality evidence*). In contrast, we recommend *against* administration of antihistamines in patients with EIB who do not have allergies (*strong recommendation*, *moderate-quality evidence*).
- For all patients with EIB, we recommend interval or combination warm-up exercise before planned exercise (*strong recommendation*, *moderate-quality evidence*).
- For patients with EIB who exercise in cold weather, we suggest routine use of a device (i.e., mask) that warms and humidifies the air during exercise (*weak recommendation*, *low-quality evidence*).
- For patients with EIB who have an interest in dietary modification to control their symptoms:
  - We suggest implementation of a low-salt diet (*weak recommendation*, *moderate-quality evidence*).
  - We suggest dietary supplementation with fish oils (*weak recommendation*, *low-quality evidence*).
  - We suggest *against* dietary supplementation with lycopene (*weak recommendation*, *low-quality evidence*).
  - We suggest dietary supplementation with ascorbic acid (*weak recommendation*, *moderate-quality evidence*).
- An algorithm summarizing diagnosis and treatment of EIB is provided in Figure 1.

INTRODUCTION

Exercise-induced bronchoconstriction (EIB) describes acute airway narrowing that occurs as a result of exercise. The exact prevalence of EIB in patients with asthma is not known, but exercise is one the most common triggers of bronchoconstriction in patients with asthma, and a substantial proportion of patients with asthma experience exercise-induced respiratory symptoms.

EIB has also been shown to occur in subjects without a known diagnosis of asthma, with prevalence of up to 20% being reported (1). As a result, this has led to controversy regarding nomenclature related to bronchoconstriction occurring as a result of exercise. Many experts advocate using the terminology "exercise-induced bronchoconstriction" instead of "exercise-induced asthma," as it does not imply that the patient has underlying chronic asthma or that exercise actually "caused" asthma. For the purposes of this document, we will use the terminology "exercise-induced bronchoconstriction" without regard to whether it occurs in patients with or without asthma.

There are substantial data showing that EIB occurs very commonly in athletes at all levels. Many studies have been performed in Olympic or elite-level athletes that have documented prevalence of EIB varying between 30 and 70%, depending on the population studied and methods implemented (1). Studies have also been done on college, high school, and recreational athletes that have shown a significant prevalence of EIB (2–4).

The symptoms of EIB are variable and nonspecific, and presence or absence of specific respiratory symptoms has very poor predictive value for objectively confirmed EIB (4, 5). Clinical presentation may include chest tightness, cough, wheezing, and dyspnea. These symptoms may only be provoked by exercise or may only occur in specific environments, such as ice rinks or indoor swimming pools. The symptoms are often mild to moderate in severity and may cause impairment of athletic performance, but are not severe enough to cause significant respiratory distress. However, severe episodes of EIB can occur, and respiratory failure and even death have occurred in rare cases (6).

Given the significant prevalence of EIB, it is critical that evidence-based documents exist to guide health care providers with regard to the pathogenesis, diagnosis, management, and treatment of EIB, as well as other critical issues related to EIB, such as environmental influences and considerations in Olympic/elite-level athletes. To provide such guidance, a multidisciplinary panel was convened to develop evidence-based guidelines.

METHODS

These guidelines were developed in accordance with the American Thoracic Society's (ATS's) standards for clinical practice guidelines (Table 1). The methods are described in detail in the online supplement.

PATHOGENESIS

A modest period of high-intensity exercise or, alternatively, increased minute ventilation during isocapnic hyperpnea triggers a prototypical response consisting of bronchoconstriction, which occurs predominantly after the cessation of a short period of

TABLE 1. METHODS CHECKLIST

	Yes	No
Panel assembly		
• Included experts for relevant clinical and nonclinical disciplines	X	
• Included individual who represents the views of patients and society at large		X
• Included a methodologist with appropriate expertise (documented expertise in conducting systematic reviews to identify the evidence base and the development of evidence-based recommendations)	X	
Literature review		
• Performed in collaboration with librarian	X	
• Searched multiple electronic databases	X	
• Reviewed reference lists of retrieved articles	X	
Evidence synthesis		
• Applied prespecified inclusion and exclusion criteria	X	
• Evaluated included studies for sources of bias	X	
• Explicitly summarized benefits and harms	X	
• Used PRISMA1 to report systematic review		N/A
• Used GRADE to describe quality of evidence	X	
Generation of recommendations		
• Used GRADE to rate the strength of recommendations	X	

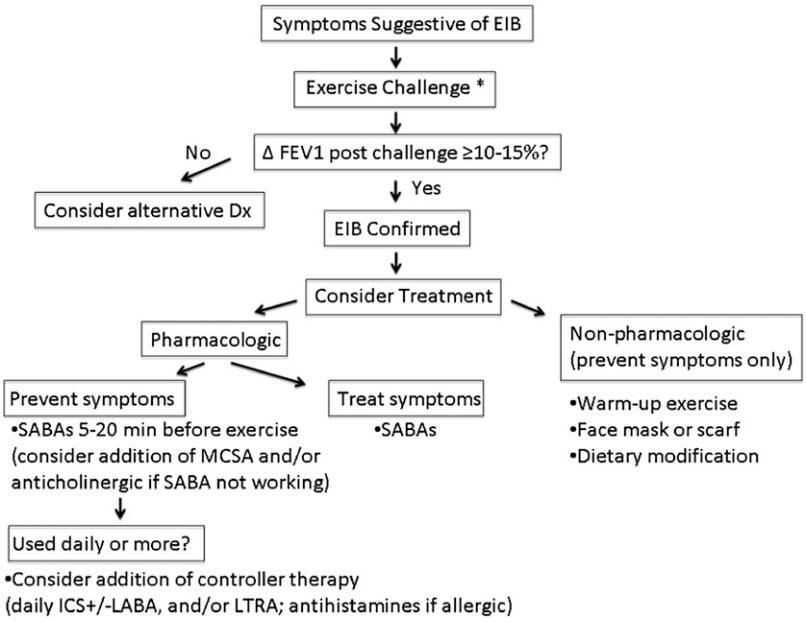

Figure 1. Diagnostic and treatment algorithm for exercise-induced bronchoconstriction. EIB = exercise-induced bronchoconstriction; ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; LTRA = leukotriene receptor antagonist; MCSA = mast cell stabilizing agent; SABA = short-acting β-agonist. *Or surrogate challenge, for example, hyperpnea or mannitol.

hyperpnea and lasts from 30 to 90 minutes in the absence of treatment. The predisposition to the development of this syndrome varies markedly among subjects with asthma, and is known to occur in some groups of subjects without asthma, such as elite athletes. Several studies indicate that subjects who are prone to EIB have increased levels of exhaled nitric oxide (7), leukotrienes (8, 9), expression of mast cell genes (10), and epithelial shedding into the airway lumen (9).

Although the events that trigger this syndrome are not fully understood, it is clear that inflammatory mediators, including histamine, tryptase, and leukotrienes, are released into the airways from cellular sources in the airways, including eosinophils and mast cells (11, 12). The activation of sensory nerves may play an important role in the pathogenesis of EIB, and may be involved in mucus release into the airways after exercise challenge (13, 14). The epithelium may play a key role in sensing the transfer of water and heat out of the lower airways, but the way in which this epithelial response leads to cellular activation by leukocytes remains incompletely understood. Each is described in detail in the online supplement.

ROLE OF THE ENVIRONMENT

The high prevalence of EIB in populations of athletes may be related to specific environmental demands of specific sports (15). For example:

- The approximate 30% prevalence of EIB reported in ice rink athletes has been linked to the inhalation of cold dry air in combination with the high emission pollutants from fossil-fueled ice resurfacing machines (16–18).
- The high prevalence of airway injury and bronchial hyperresponsiveness reported among Nordic skiers has been attributed to high ventilation inhalation of cold, dry air during training and competition (19–21).
- The 11–29% prevalence of asthma and EIB reported among competitive swimmers (22) has been associated with the high levels of trichloramines in the indoor pool air (23–25). The prevalence of EIB among distance runners is higher than that of the general population, and has been attributed to exercising in high allergen (26) and high ozone environments (27).

Among the environmental exposures that have been proposed to contribute to EIB are cold air, dry air, ambient ozone, and airborne particulate matter. Susceptible populations, such as children and those with pre-existing cardiovascular disease, diabetes, or lung disease, are more sensitive to an acutely increased fraction of particles deposited in the lungs during exercise. Evidence supports increased airway hyperresponsiveness and decreased lung function from chronic exposure to air pollutants during exercise. The effects of each exposure and the evidence for each are described in detail in the online supplement.

DIAGNOSIS

The diagnosis of EIB is established by changes in lung function after exercise, not on the basis of symptoms. Symptoms that are often associated with vigorous exercise, such as shortness of breath, cough, wheeze, and mucus production, are neither sensitive nor specific for identifying those with EIB (4, 5, 28). Among athletes with and without symptoms associated with exercise, EIB can be identified in individuals without symptoms, and many individuals with respiratory symptoms will not have EIB (4, 5, 28–31).

Measuring and Quantifying EIB

Serial lung function measurements after a specific exercise or hyperpnea challenge are used to determine if EIB is present and to quantify the severity of the disorder. It is preferable to assess FEV_1, as this measurement has better repeatability (32) and is more discriminating than peak expiratory flow rate (33–35). The measurement of $FEV_{0.5}$ (in 3- to 6-year-old children) and airway resistance using the interrupt technique (in 5- to 12-year-old children) have been used successfully to establish a diagnosis of EIB (36, 37). Recovery from EIB is usually spontaneous, and FEV_1 returns to 95% baseline value within 30–90 minutes. In a group of 7- to 12-year-old children, recovery occurred faster in the younger children (38).

According to ATS/European Respiratory Society guidelines, at least two reproducible FEV_1 maneuvers are measured serially after exercise challenge, with the highest acceptable value recorded at each interval (39, 40). FEV_1 is usually measured at 5, 10, 15, and 30 minutes after exercise, but may be more

frequent if a severe response is expected. An FVC maneuver is not required, as repeated efforts may tire the subject. The airway response is expressed as the percent fall in FEV_1 from the baseline value. The difference between the pre-exercise FEV_1 value and the lowest FEV_1 value recorded within 30 minutes after exercise is expressed as a percent of the pre-exercise value (40). The criterion for the percent fall in FEV_1 used to diagnose EIB is ⩾10% in some guidelines (40–43). The ⩾10% fall value was based on the mean plus two SDs of the percent fall in FEV_1 in normal healthy subjects without a family history of asthma, atopy, or recent upper respiratory tract infection (35, 44, 45). Higher values for percent fall in FEV_1 (i.e., 15 and 13.2%) have been recommended for diagnosing EIB in children (46–48). A fall of ⩾10% at two consecutive time points has been recommended (49). Many laboratories use a criterion of ⩾15% from baseline because of the greater specificity of this criterion. The reproducibility of EIB as determined by two separate tests is good, with 76% agreement between tests. The response in FEV_1 (percent decline) is ±14.6% when both tests demonstrate a ⩾10% fall, and ±15.7% when only one test demonstrates a ⩾10% fall. Thus, two tests may be required when using exercise to exclude a diagnosis of EIB (44). The severity of EIB can be graded as mild, moderate, or severe if the percent fall in FEV_1 from pre-exercise level is ⩾ 10% but <25%, ⩾25% but <50%, and ⩾50%, respectively (50–52). This grading was based on the range of measured values for EIB and before the widespread use of inhaled steroids. Currently, a decline in FEV_1 of ⩾30% in a person taking inhaled steroids would be considered severe.

Exercise Challenge Testing to Identify EIB

The type, duration, and intensity of exercise and the temperature and water content of the air inspired are important determinants of the airway response to exercise (53–60). The time since the last exercise is also important, because some subjects become refractory to another exercise stimulus for up to 4 hours (61–63). The two most important determinants of EIB are the sustained high-level ventilation reached during exercise and the water content of the air inspired (54, 55, 64–67). The ventilation required for a valid test is at least 17.5 times FEV_1 and preferably greater than 21 times FEV_1 (68). Measurement of ventilation during testing for EIB permits comparisons to be made on the effect of the same stimulus over time and between subjects (68). Although heart rate is often used as a surrogate measure of the intensity of exercise, the relationship between heart rate and ventilation varies widely based on fitness and other factors (69).

The ideal protocol to detect EIB involves a rapid increase in exercise intensity over approximately 2–4 minutes to achieve a high level of ventilation. Most protocols recommend breathing dry air (<10 mg H_2O/L) with a nose clip in place while running or cycling at a load sufficient to raise the heart rate to 80–90% of predicted maximum (predicted maximum heart rate ≈ 220 − age in years) (44, 47, 48, 69–71) or ventilation to reach 17.5–21 times FEV_1 (68, 72, 73). Once this level of exercise is attained, the subject should continue exercise at that high level for an additional 4–6 minutes. These targets are more rapidly achieved with running exercise compared with cycling. Sports-specific exercise is probably the most relevant for elite athletes that can be tested during the activity that causes symptoms (28). The use of short-acting and long-term preventative asthma medications (68, 72, 73), recent intense or intermittent warm-up exercise (61–63), recent use of nonsteroidal anti-inflammatory medication (74), and recent exposure to inhaled allergens may alter the severity of the response to exercise challenge (75–77).

Surrogates for Exercise to Identify EIB

A number of surrogates for exercise testing have been developed that may be easier to implement than dry air exercise challenge. These surrogates include eucapnic voluntary hyperpnea of dry air and inhalation of hyperosmolar aerosols of 4.5% saline or dry powder mannitol. Although none of these surrogate tests are completely sensitive or specific for EIB, they all have utility for identifying airway hyperresponsiveness consistent with a diagnosis of EIB (4, 78–88). The surrogates of exercise are described in detail in the online supplement.

TREATMENT

Treatment for EIB can be broken down into pharmacologic and nonpharmacologic therapy. Currently used pharmacologic therapy includes short-acting β_2-agonists (SABAs) and long-acting β_2-agonists (LABAs), leukotriene receptor antagonists (LTRAs), and inhaled corticosteroids (ICSs). Mast cell stabilizing agents (MCSAs) have traditionally been used to treat EIB, and, although these agents are no longer available in the United States, they remain available in other countries around the world. Other drugs, such as inhaled anticholinergic agents (ipratropium) and antihistamines, may play a minor role in treating some patients with EIB. Nonpharmacologic therapy includes warm-up to induce a refractory period, maneuvers to prewarm and humidify the air during exercise (e.g., breathing through a face mask or scarf), improving general physical conditioning, losing weight if obese (89), and modifying dietary intake. The goals of therapy are to relieve bronchoconstriction should it occur and to minimize or prevent bronchoconstriction from happening in the first place, thus allowing the athlete or patient with EIB to continue to engage in physical activity or sports with minimal respiratory symptoms.

Questions and Recommendations

Question 1: *Should patients with EIB be treated with an inhaled SABA before exercise?*

The most common therapeutic recommendation to minimize or prevent symptoms of EIB is the prophylactic use of short-acting bronchodilators (β_2-agonists), such as albuterol, shortly before exercise (90). These agents work by stimulating β_2-receptors on airway smooth muscle, causing muscle relaxation and bronchodilation, as well as possibly preventing mast cell degranulation. SABAs, given by inhalation 5–20 minutes before exercise, are usually effective for 2–4 hours in protecting against or attenuating EIB (91, 92), but may fail to prevent bronchoconstriction in 15–20% of patients with asthma (72). In addition, daily use of β_2-agonists alone or in combination with ICSs may lead to tolerance, manifested as a reduction in duration of protection against EIB, and a prolongation of recovery in response to SABA after exercise (93, 94). Tolerance is thought to be due to desensitization of the β_2-receptors on mast cells and airway smooth muscle. This is why β_2-agonists are generally only used on an intermittent basis for prevention of EIB, and why patients who use SABAs on a more regular basis (e.g., daily) are generally started on a controller agent, such as ICS or LTRAs.

Our recommendation for an inhaled SABA before exercise is based upon a systematic review of the literature that identified eight randomized trials, of which five were pooled. Patients who received an inhaled SABA had a maximum percent fall in FEV_1 after exercise that was 26.03% less than that among patients who received placebo. The large magnitude of effect was not offset by risk of bias, indirectness, inconsistency, or imprecision. Thus, the evidence provided high confidence in the estimated effects of inhaled SABA. The recommendation is strong,

because the committee is certain that the reduction of breathlessness associated with the lower maximum percent fall in FEV_1 after exercise outweighs the relatively minor potential side effects, burdens, and cost of pre-exercise SABA therapy (*see* Table E1 in APPENDIX 2).

Recommendation 1: *For patients with EIB, we recommend administration of an inhaled SABA before exercise* (*strong recommendation, high-quality evidence*). *The inhaled SABA is typically administered 15 minutes before exercise. Such use should be less than daily, on average.*

Question 2: *Should patients with EIB be treated with an inhaled LABA?*

A controller agent is typically added whenever SABA therapy is used on a daily basis or more frequently. LABAs are effective in treating and preventing EIB (72, 95); however, similar to the use of SABAs, the protective effect afforded by LABAs decreases with daily use (96–98). Although LABAs may initially protect against bronchoconstriction for 6–12 hours, the effect diminishes to lasting only 6 hours after daily use for 30 days (97). Unfortunately, concomitant use of daily ICS does not mitigate this loss of effectiveness (96, 98). One study found that formoterol remained effective as long as it was used three times per week or less; so, as a single agent, LABAs may be used for EIB at this frequency (99). However, there remains serious concern about increased morbidity and mortality with any use of LABAs as monotherapy, without concomitant ICS in patients with asthma (100, 101).

Our recommendation against daily LABA monotherapy is based upon our review of the literature, which identified two relevant randomized trials (102, 103). Both trials compared LABA monotherapy to placebo after the withdrawal of ICSs and found an increased rate of treatment failures and acute exacerbations among those receiving LABA monotherapy.

Other randomized trials and meta-analyses that evaluated LABA therapy were also identified; however, most included patients who were receiving concomitant ICSs. The studies that either included a large proportion of patients receiving LABA as monotherapy or analyzed patients who were receiving LABA monotherapy separately supported the potential for increased adverse effects among those receiving LABA monotherapy (100, 101).

This evidence provides moderate confidence in the estimated effects of LABA monotherapy, because the randomized trials had indirectness (i.e., the trials included patients with asthma in general, not patients with EIB specifically). The recommendation against daily LABA therapy is strong, because the importance of the potential downsides of LABA monotherapy (i.e., serious adverse effects, including asthma-related mortality, exacerbations requiring hospitalization, cost, and burdens) substantially outweigh the upsides (i.e., less dyspnea, less need for inhaled SABAs), particularly in light of the availability of safer alternative therapies.

Recommendation 2: *For patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we recommend* against *daily use of an inhaled LABA as single therapy* (strong recommendation, moderate-quality evidence).

Question 3: *Should patients with EIB be treated with ICSs?*

Daily ICSs are considered the most effective anti-inflammatory agents for EIB (104). This may be due not only to better control of underlying asthma, but perhaps to a direct therapeutic effect on airway inflammation that is associated with EIB (11, 105, 106). ICS can be used alone or in combination with other treatments for EIB. As mentioned previously here, ICS therapy does not prevent the occurrence of tolerance from daily β_2-agonist use. Studies on inhaled steroids have shown that the maximum beneficial effect in protecting against EIB may take as long as 4 weeks, and is dose dependent (104, 107). Although a single high dose of beclomethasone dipropionate has been shown to have a protective effect against hyperpnea-induced bronchospasm, this strategy is not recommended clinically (108). Interestingly, ICS do not seem to be as protective in elite athletes without asthma who experience EIB compared with patients with asthma with EIB (109). As with all inhaled medications, proper inhaler technique must be taught to the patient and reinforced at follow-up visits.

Our recommendation for a *daily* ICS is based upon a systematic review that found six randomized trials, of which four were pooled. Patients with EIB who received a daily ICS had a mean maximum percent fall in FEV_1 after exercise that was 10.98% less than that seen among patients who received placebo. The randomized trials were limited by imprecision (i.e., the ends of the confidence intervals led to different clinical decisions), providing moderate confidence in the estimated effects. The recommendation is strong because the committee is certain that the reduction of dyspnea associated with the decrease in the maximum percent fall in FEV_1 after exercise outweighs the relatively minor burdens, cost, and side effects of ICS therapy (*see* Table E2A in APPENDIX 2).

Our recommendation against *pre-exercise* ICS is based upon a systematic review that identified four randomized trials, of which two were pooled. Patients with EIB who received pre-exercise ICS had a mean maximum percent fall in FEV_1 after exercise that was similar to that seen among patients who received placebo. The randomized trials were limited by imprecision, providing moderate confidence in the estimated effects. The recommendation is strong because the committee is certain that the downsides of pre-exercise ICS exceed the upsides. There appear to be no significant benefits, but there are potential side effects, costs, and burdens (*see* Table E2B in APPENDIX 2).

Recommendation 3A: *For patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we recommend daily administration of an ICS* (strong recommendation, moderate-quality evidence). *It may take 2–4 weeks after the initiation of therapy to see maximal improvement.*

Recommendation 3B: *For the same patients, we recommend* against *administration of ICS only before exercise* (strong recommendation, moderate-quality evidence).

Question 4: *Should patients with EIB be treated with LTRAs?*

LTRAs, such as montelukast, given once daily, will reduce EIB and also improve the recovery to baseline. There is no development of tolerance when taken daily (110). The magnitude of effect may be smaller for LTRAs than either ICS or pre-exercise SABA. However, the duration of action is longer, lasting up to 24 hours, which may be very useful for patients or athletes engaging in physical activity throughout the day (111, 112). LTRAs should be taken at least 2 hours before exercise to have a maximal prophylactic effect (111). LTRAs appear to protect against EIB regardless of whether patients have asthma or are elite athletes without asthma (113).

Our recommendation for a daily LTRA is based upon a systematic review that identified 11 randomized trials, of which 7 were pooled. Patients with EIB who received a daily LTRA had a mean maximum percent fall in FEV_1 after exercise that was 10.70% less than that seen among patients who received placebo. The randomized trials were limited by imprecision, providing moderate confidence in the estimated effects. The recommendation is strong because the committee is certain that the reduction of dyspnea associated with the decrease in the

maximum percent fall in FEV_1 after exercise outweighs the comparatively minor burdens, cost, and side effects of LTRA therapy (*see* Table E3 in APPENDIX 2).

The choice of whether to add daily ICS or daily LTRA to as-needed use of SABA in patients with EIB who do not respond to intermittent SABA therapy alone, in most cases, is a personal one that should be made on a case-by-case basis. Strictly speaking, the evidence supports efficacy of both types of medications in EIB, although ICS therapy may have a more potent anti-inflammatory effect in patients with EIB associated with airway inflammation. This may be relevant to the patient with asthma with EIB as opposed to the elite athlete without asthma with EIB, in whom ICS may work better in the former. In cases where baseline lung function is below normal, guidelines recommend use of ICS initially (90). Both classes of medicines are readily available in the United States in contrast to MCSAs. Some patients would prefer to avoid using an inhaler and avoid using daily ICS; in these situations, trying a daily LTRA would be reasonable, or, if not exercising daily, then using montelukast at least 2 hours before planned exercise. Other patients may prefer to use inhaled ICS because they want to avoid any potential systemic effects of daily LTRA therapy; in these cases, trying daily ICS would be reasonable. In all cases, it is always essential to ensure that underlying asthma is under control, and continued and close follow up with the patient is important to achieve therapeutic effect on minimal and acceptable medication.

Recommendation 4: *For patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we recommend daily administration of an LTRA* (strong recommendation, moderate-quality evidence).

Question 5: *Should patients with EIB be treated with an MCSA?*

MCSAs, such as sodium cromoglycate and nedocromil sodium, provide protection against EIB by blocking degranulation of mast cells and release of mediators, such as prostaglandin D_2. Cochrane Reviews (114, 115) have demonstrated consistent protection against EIB, with an attenuation of EIB by about 50%. There are no significant differences between sodium cromoglycate and nedocromil sodium. MCSAs appear to be more effective at attenuating EIB than anticholinergic agents, but less effective than SABAs. There appears to be no advantage to combining MCSAs with SABAs, as the effects are similar to using SABAs alone.

Our recommendation for an MCSA before exercise is based upon a systematic review that identified 24 randomized trials, of which 20 were pooled. Patients with EIB who received an MCSA before exercise had a mean maximum percent fall in FEV_1 after exercise that was 15.20% less than that seen among patients who received placebo. The randomized trials had no serious risk of bias, indirectness, inconsistency, or imprecision, thereby providing a high degree of confidence in the estimated effects. The recommendation is strong because the committee is certain that the reduction of dyspnea associated with the decrease in the maximum percent fall in FEV_1 after exercise outweighs the comparatively minor burdens, cost, and side effects of pre-exercise MCSA therapy (*see* Table E4 in APPENDIX 2).

Although the evidence for MCSAs is high quality, it is important to note that the lack of availability of these medications in the United States may make this recommendation less clinically applicable in the United States, although they are readily available worldwide.

Recommendation 5: *For patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we recommend administration of an MCSA before exercise* (strong recommendation, high-quality evidence).

Question 6: *Should patients with EIB be treated with an antihistamine?*

Antihistamines have been studied as a treatment for EIB. The results of these studies are variable, with some protection against EIB seen in a small percentage of patients (116, 117). The inconsistency in the data may be due to differences in the severity of EIB studied and the ability of terfenadine, used in some of the positive studies, to also inhibit leukotrienes, thus confounding the specific role of an antihistamine effect (118). Because controlling allergies in patients with atopy with asthma leads to better asthma control in general, it seems prudent that allergic patients with asthma with EIB may benefit from antihistamine therapy (119).

A systematic review of the evidence identified three randomized trials, which were pooled. Patients with EIB who received a daily antihistamine had no significant decrease in their mean maximum percent fall in FEV_1 after exercise compared with patients who received placebo. The randomized trials were limited by imprecision, providing moderate confidence in the finding of no effect (*see* Table E5 in APPENDIX 2).

Our recommendation for daily antihistamine therapy in allergic patients indicates the committee's belief that antihistamines may be helpful in EIB, as controlling allergies improves asthma control in general. The weak strength of the recommendation reflects the uncertainty about the balance of potential benefits versus harms, burdens, and cost, as the relevant trials did not analyze individuals with atopy separately.

In contrast, our recommendation against antihistamines in nonallergic individuals is strong because the committee is certain that the downsides exceed the upsides. Antihistamines appear to confer no significant benefits in such patients, but have potential side effects, costs, and burdens.

Recommendation 6A: *For patients with EIB and allergies who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we suggest using an antihistamine to prevent EIB* (weak recommendation, moderate-quality evidence).

Recommendation 6B: *For nonallergic patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise, or who require an inhaled SABA daily or more frequently, we recommend* against *using antihistamines* (strong recommendation, moderate-quality evidence).

Question 7: *Should patients with EIB be treated with a short-acting inhaled anticholinergic?*

Like antihistamines, anticholinergic treatment with ipratropium has variable effects on preventing or treating EIB. Our recommendation for administration of an inhaled short-acting anticholinergic agent before exercise is based upon a published systematic review of 12 randomized trials, all of which were pooled (115). Patients with EIB who received inhaled ipratropium bromide before exercise had a mean maximum percent fall in FEV_1 after exercise that was 9.80% less than that seen among patients who received placebo. The evidence was limited by inconsistent results and imprecision, providing low confidence in the estimated effects. The recommendation is weak because the committee is uncertain that the reduction of dyspnea associated with the decrease in the maximum percent fall in FEV_1 after exercise outweighs the potential side effects, burdens, and cost. The uncertainty derives from the small effect size and the low quality of evidence (*see* Table E6 in APPENDIX 2).

Recommendation 7: *For patients with EIB who continue to have symptoms despite using an inhaled SABA before exercise,*

or who require an inhaled SABA daily or more frequently, we suggest administration of an inhaled anticholinergic agent before exercise (weak recommendation, low-quality evidence).

Question 8: *Should patients with EIB engage in a physical activity before exercise, to induce a refractory period?*

An important nonpharmacologic strategy to minimize EIB used by many athletes is to engage in physical warm-up before the planned period of exercise or competition (62, 63, 120, 121). Typically, the warm-up consists of 10–15 minutes of moderately vigorous exercise, and subsequent EIB is reduced for the next 2 hours, resulting in a so-called "refractory period." This phenomenon does not occur in all athletes, and may not occur at all in athletes without asthma with EIB. Various approaches, including low-intensity, high-intensity, interval, or continuous exercise, and combinations of these, have been tried (93). A recent review of this subject suggests that a warm-up consisting of variable high-intensity exercise, as opposed to continuous high- or low-intensity exercise, appears to be the most effective strategy to attenuate EIB (122).

Our recommendation for interval or combination warm-up exercise before planned exercise is based upon a published systematic review of four randomized trials of interval warm-up, three randomized trials of low-intensity continuous warm-up, two randomized trials of high-intensity continuous warm-up, and two randomized trials of combination warm-up (115). Patients with EIB who underwent interval, low-intensity continuous, high-intensity continuous, or combination warm-up before exercise had a mean maximum percent fall in FEV_1 after exercise that was 10.61, 12.60, 7.97%, and 10.94% less than that seen among patients who did not undergo formal warm-up, respectively. These improvements were statistically significant only for interval and combination warm-up.

The evidence for interval and combination warm-up was limited by imprecision, providing moderate confidence in the estimated effects. In contrast, the evidence for low-intensity and high-intensity continuous warm-up was limited by inconsistent results and imprecision, providing low confidence in the estimated effects (*see* Tables E7A–E7D in Appendix 2). The recommendation is strong, because the committee is certain that the reduction of dyspnea associated with the decrease in the maximum percent fall in FEV_1 after interval and combination warm-up exercise and the effects of warm-up on injury prevention outweigh the burden and risks of the warm-up exercise.

General physical conditioning may also help attenuate EIB (89). This likely occurs not on the basis of any direct effect on lung function, but, rather, indirectly due to the lower minute ventilation required for any given workload once cardiovascular conditioning has been improved.

Recommendation 8: *For all patients with EIB, we recommend interval or combination warm-up exercise before planned exercise* (strong recommendation, moderate-quality evidence).

Question 9: *Should patients with EIB use a device to warm or humidify the air when they exercise in cold weather?*

Another technique to minimize EIB symptoms is to prewarm and humidify the inhaled air. This strategy follows from the concept that bronchoconstriction in EIB occurs as a result of the cooling and drying of the airways during the high minute ventilation of exercise. Two strategies that have been employed are breathing through the nose (123) and use of a facemask (124). In one study, breathing through a heat exchanger mask was as effective as albuterol in preventing EIB (125).

Our recommendation to use a device that warms and humidifies air during exercise in cold weather is based upon a systematic review that found a randomized trial and two nonrandomized controlled trials. In the randomized trial, patients with EIB who used a device to warm and humidify air had a mean maximum percent fall in FEV_1 after exercise that was 14.70% less than that seen among patients who did not use such a device. The trial was limited by risk for bias and imprecision, providing low confidence in the estimated effects. The result of the randomized trial was consistent with both nonrandomized controlled trials. The weak strength of the recommendation reflects uncertainty about the degree of benefit—uncertainty that derives from the low quality of evidence (*see* Table E8 in Appendix 2).

Recommendation 9: *For patients with EIB who exercise in cold weather, we suggest the routine use of a device (i.e., mask) that warms and humidifies the air during exercise* (weak recommendation, low-quality evidence).

Question 10: *Should patients with EIB change their dietary habits (e.g., low-salt diet, fish oil supplementation, lycopene, vitamin C)?*

There have been many studies examining the effects of dietary modification on EIB (126–134). Low-sodium diet (130), fish oil (omega-3 polyunsaturated fatty acids) supplementation (131), oral lycopene (132), and ascorbic acid supplementation (1,500 mg/day) (129) have all been studied in relation to EIB. All were found to have some effect in reducing the severity of EIB, but all of these studies had important limitations, so their findings should be considered preliminary until confirmed in larger trials. With regard to fish oil, there may be a differential effect of treatment depending on whether the patient has underlying asthma (in which case, the fish oil supplementation may not attenuate EIB) (133) or not (in which case, fish oil supplementation may attenuate EIB) (134, 135). Given the lack of obvious risk to patients in administering these adjunctive therapies, it is reasonable to try them in interested patients, but the evidence is not strong enough to conclude that they are effective in a large majority of patients with EIB.

Our recommendation for a low-salt diet is based upon a systematic review that identified six randomized trials, which could not be pooled due to insufficient reporting of the crude data. In all of the trials, however, patients with EIB who received a low-salt diet had a significantly smaller decrease in the mean maximum percent fall in FEV_1 after exercise than patients who did not receive a low-salt diet. These trials provided moderate confidence in the estimated effect, because they were limited by imprecision (*see* Table E9A in Appendix 2).

Our recommendation for fish oil supplementation is based upon a systematic review that identified one relevant randomized trial in which patients with EIB who received fish oil supplementation had a mean maximum percent fall in FEV_1 after exercise that was 11.50% less than that seen among patients who did not receive fish oil supplementation. The evidence provided low confidence in the estimated effect because it was limited by imprecision and inconsistency (a subsequent trial that measured different outcomes found no effect). *See* Table E9B in Appendix 2.

Our recommendation against lycopene supplementation is based upon a systematic review that identified two relevant randomized trials. In one trial, patients with EIB who received lycopene had a mean maximum percent fall in FEV_1 after exercise that was 11.80% less than that seen among patients who did not receive lycopene. In contrast, the other trial found no effect from lycopene supplementation. The evidence provided low confidence in the estimated effect because of the inconsistency of the results and imprecision (*see* Table E9C in Appendix 2).

Our recommendation for ascorbic acid (i.e., vitamin C) supplementation is based upon a systematic review that identified two relevant randomized trials. In both trials, patients with

EIB who received ascorbic acid supplementation had a mean maximum percent fall in FEV_1 after exercise that was approximately half of that seen among patients who did not receive ascorbic acid supplementation. The evidence provided moderate confidence in the estimated effect because it was limited by imprecision (*see* Table E9D in APPENDIX 2).

All of the recommendations are weak because the committee is uncertain that the reduction of dyspnea associated with dietary supplementation outweighs the burden of dietary modification. This uncertainty derives from the limitations of the supportive evidence.

Recommendation 10A: *For patients with EIB who have an interest in dietary modification to control their symptoms, we suggest a low-salt diet* (weak recommendation, moderate-quality evidence).

Recommendation 10B: *For patients with EIB who have an interest in dietary modification to control their symptoms, we suggest dietary supplementation with fish oils* (weak recommendation, low-quality evidence).

Recommendation 10C: *For patients with EIB who have an interest in dietary modification to control their symptoms, we suggest* against *dietary supplementation with lycopene* (weak recommendation, low-quality evidence).

Recommendation 10D: *For patients with EIB who have an interest in dietary modification to control their symptoms, we suggest dietary supplementation with ascorbic acid* (weak recommendation, moderate-quality evidence).

General Comments Regarding Therapy

Our overall recommendations regarding therapy leave a lot of options for the individual patient, which should be discussed with the patient's physician and tried and evaluated on an ongoing basis. The mainstay of therapy remains maintaining good control of underlying asthma (if present) and preventing or treating symptoms of EIB with SABAs. If such therapy does not work, then the next best options are to add daily ICS or daily LTRA, depending on patient preference. After this, the patient may try adding or substituting with inhaled mast cell stabilizing, anticholinergic, or oral antihistamine therapy. Pre-exercise warm-up is recommended for all patients, as is wearing a mask or scarf in cold weather for those with cold weather–induced symptoms. Improving physical fitness and losing weight if obese seem prudent. Finally, although there is not a lot of evidence to support dietary modification, patients with an interest in this approach may try a low-salt diet, or supplementing with fish oil or vitamin C. The addition of lycopene is not strongly supported.

SCREENING FOR EIB

Screening is defined as the strategy used in a population to detect a condition in a preclinical or asymptomatic phase with the aim of providing timely intervention to favorably influence outcome. In contrast, case detection is the identification of individuals with disease who are symptomatic, but undiagnosed.

A number of organizations and investigators advocate screening for asthma in both the general population (136) and in athletes (137–139), yet evaluation of screening based upon the World Health Organization criteria (described in the online supplement) reveals important deficiencies in the data required to ensure the validity of this approach (140, 141). Accordingly, an ATS report on screening for asthma that was published in 2007 concluded that there was insufficient evidence to support the adoption of population-based asthma case detection, based primarily upon a lack of detail regarding health outcome (142). It was, however, felt that case detection programs may be appropriate in areas where there is a high prevalence of undiagnosed asthma, and where newly detected cases have access to high-quality care. This recommendation is pertinent to the athletic population, and, indeed, some sporting organizations have established EIB screening programs for their internationally competitive athletes (137, 143). Yet, to date, expert working groups have not directly addressed EIB screening policy (1, 41, 144).

We were unable to locate any randomized controlled trials or large, well done observational studies (i.e., case control, cohort studies) evaluating the overall efficacy of a screening program for EIB on either health or performance outcome. Such studies are difficult to conduct (145), but, nevertheless, they remain a prerequisite for a rigorous evaluation of a screening policy. Therefore, there presently remains major uncertainty in the estimates of benefits, harms, and burdens of a screening/case detection policy for EIB. For individuals who engage in athletic activity, more evidence is needed before the value of screening for EIB can be determined.

There is a small number of observational studies in which population subgroups or athletic teams have undergone an EIB "screening" assessment. These evaluations have typically involved athletic individuals who were members of competitive sporting associations (138, 146, 147), and were predominately conducted with the aim of evaluating prevalence and/or the utility of detection methods as opposed to a direct appraisal of a screening policy. Extrapolating the findings of these studies, which primarily involve referred, selected populations, to a general screening policy is inappropriate, but does provide insight to target further work evaluating the feasibility and potential methodological limitations of screening for EIB. The studies are described separately in the online supplement.

EXERCISE, ASTHMA, AND DOPING

Doping is defined as the use of any banned substance (including drugs and blood products) to improve athletic performance. The International Olympic Committee maintains a list of "substances and methods prohibited in-competition, out-of-competition and in particular sports." Many of the standard therapies employed to treat EIB have restricted use in competitive athletes, and it is important for athletes and healthcare providers to be aware of these restrictions (www.globaldro.com).

For example, all β_2-agonists are banned in competition except short-acting inhaled albuterol (salbutamol) and LABAs salmeterol and formoterol. Other inhaled LABAs may be added in the future. Some LABAs, such as clenbuterol, have been shown to enhance athletic performance and are banned entirely from use both in and out of competition based on their anabolic capacities. Beginning in 2010, the use of albuterol and salmeterol by inhalation no longer requires a therapeutic use exemption (TUE). As of January 1, 2013, inhaled formoterol up to a maximum dose of 54 μg/24 hours is no longer prohibited and, hence, does not require a TUE. The therapeutic maximum daily dosage of albuterol is 1,600 μg/24 h by inhalation (148, 149). When albuterol is found in urine in excess of 1,000 ng/ml, it is presumed that the albuterol was not intended to be used therapeutically and is considered an adverse analytical finding unless pharmacokinetic data are available in the athlete to refute the finding to demonstrate otherwise. All β_2-agonists are prohibited if administered orally or by injection.

All glucocorticoids are prohibited when given by oral, intravenous, or intramuscular route. Inhaled steroids are permitted, as are oral and inhaled treatments with LTRAs, cromones (not readily available in the United States), and muscarinic receptor antagonists. None of these agents enhance performance in athletes without asthma and, therefore, they do not require a TUE (150, 151).

The history of the International Olympic Committee and World Anti-Doping Agency policies are described in the online supplement.

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